UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

7/18/00

MEMORANDUM

SUBJECT: **Vinclozolin.** Agency Response to BASF Corporation's Comments on the February 14, 2000 Preliminary Human Health Risk Assessment (Chemical I.D. No. 113201)

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TO: OPP Public Docket

Attached are the Agency's responses to the 3/16/00 comments submitted by BASF Corporation on the 2/14/00 Preliminary Human Health Risk Assessment for **Vinclozolin**. Note that the Agency's response to comments relating to the drinking water and ecological assessments can be found in the 4/5/00 memo from N.E. Federoff and Dirk F. Young.

BASF Comments (paraphrased) and Agency Responses

BASF Comment 1. Given the degree of refinement in the acute dietary risk assessment (anticipated residue information was derived from residue field trials) BASF believes that regulation at the 99th percentile should be adequate to satisfy the FQPA criteria of reasonable certainty of no harm.

Response to Comment 1. Although the degree of exaggeration related to use of field trial data cannot be determined at this time, the reasons why EPA believes the dietary risks are exaggerated can be described qualitatively. These reasons include the following:

(1) Use of field trial data in the dietary risk assessment assumes that all crops are treated at the maximum application rate and harvested at the minimum PHI. In practice, crops are sometimes treated at lower application rates and harvested at

longer PHIs leading to lower residues in these crops.

(2) Use of field trial data assumes no decline in residues between harvest and consumption of the crop. However, residues of vinclozolin will decline between harvest and consumption. Data are not available to quantify the extent of this decline.

(3) Home "processing" was not accounted for in the vinclozolin dietary risk assessment. Practices such as washing, peeling, and cooking could lead to significantly lower residues than those from field trials used in the risk assessment.

(4) The vinclozolin metabolites of greatest concern are those closely related to the parent compound. Use of field trial data in the acute dietary assessment assumes that all residues have structures closely related to the parent compound and thus that they all elicit the developmental effects of concern. In reality, many metabolites convertible to 3,5-DCA may have structures sufficiently different from parent that they are not of acute concern.

Although the Agency cannot quantify for vinclozolin the combined residue reduction from these factors, for many pesticides the difference in residues between field trial and monitoring data can be an order of magnitude (10X) or more. EPA will take these factors into consideration when making risk management decisions based on acute dietary risk.

BASF Comment 2. The Agency should use the margin of exposure approach rather than the linear dose response model (Q*) to calculate the carcinogenic risk from vinclozolin.

Response to Comment 2. In 1997, the Cancer Peer Review Committee recommended that for the purposes of dose-response assessment and characterization, a non-linear approach using margin of exposure (MOE) based on a NOAEL for anti-androgenic-related effects should be used for quantitation of potential human cancer risk. The CARC met again in April, 2000 and concluded that infants, children, and adults are protected from testicular Leydig cell tumors (TLCT) through a non-linear assessment with a point of departure of 3 mg/kg/day and a margin of exposure (MOE) of 1000 (10X for intraspecies extrapolation; 10X for interspecies variation; and 10X for FQPA. However, on May 9, 2000, the FQPA Safety Factor Committee concluded that the Chronic Population Adjusted Dose (cPAD) would be protective against both potential carcinogenic effects and developmental/reproductive effects. The Committee members reasoned that, because of the relationship between vinclozolin's anti-androgenic properties and its carcinogenic effects, protecting against the anti-androgenic effects (i.e., the mode of action) would also be protective against potential carcinogenic effects to all population subgroups (including infants and children).

Accordingly, the FQPA SFC concluded that the Chronic Population Adjusted Dose would be protective against both potential carcinogenic effects and developmental/reproductive effects. The cPAD incorporates the full, additional FQPA 10X safety factor for the protection of infants and children (i.e., it is derived from the NOAEL of 1.2 mg/kg/day with a

composite uncertainty / safety factor of 1000 - 10X for intraspecies extrapolation; 10X for interspecies variation; and 10X for FQPA - see Attachment 1). Because this approach (using the cPAD) would be more protective than the proposed POD for cancer risk assessment of 3 mg/kg/day, and includes an additional 10X factor for the protection of infants and children, a separate non-linear risk assessment for cancer is not necessary.

BASF Comment 3. BASF believes that a processing factor should be applied to the residue data input file when exposure to wine reflecting treatment of wine grapes is calculated. BASF also believes that the Agency has significantly overstated the % crop treated/imported estimates for wine grapes.

Response to Comment 3. On June 28, 2000, estimates for percent of wine imports treated with vinclozolin were updated in a memo from Steve Nako, Biological and Economic Analysis Division, based on market share information submitted by BASF in April, 2000.

The processing factor issue was raised for vinclozolin in a 8/26/98 HED/OPP's Chemistry Science Advisory Council (ChemSAC) meeting. The ChemSAC decided that use of a grape juice processing factor to calculate red wine residue values is inappropriate because the processes are distinctly different in the following ways: (i) juice is rapidly squeezed from whole grapes whereas red wine involves steeping/fermenting the crushed whole grapes for several weeks which could result in distinctly different metabolic profiles and/or partitioning ratios and (ii) juice is typically pasteurized whereas wine is not which could result in a greater degree of degradation occurring in juice than in wine. ChemSAC felt that use of a juice processing factor would be acceptable for translation to white wine, provided a pasteurization step is **not** included, because white wine grape skins are rarely present during the fermentation. Note, however, that for the differences in processing factors to have any utility, distinction must be made between the consumption of white vs. red wine (and percent of each imported, if applicable) during dietary risk assessment. If no residue data are available for wine, the default concentration factor in DEEM for wine/sherry should be maintained in the dietary risk assessment.

In response to the ChemSAC's decision, the Agency asked BASF for information on the percent of white wine versus red wine imported into the U.S. However, the revised percent of wine imports imformation rendered the risk contribution of wine in the acute dietary risk assessment no longer significant. Therefore, it became unnecessary to refine residue values by breaking out white vs. red wine and applying a processing factor to white wine.

BASF Comment 4. BASF believes that the EPA-calculated dislodgeable foliar residue decline curves used in the post-application occupational risk assessment do not fit the data. Restricted entry intervals should be recalculated using a regression equation which better fits the data.

Response to Comment 4. The Agency evaluated additional statistical information submitted by BASF on April 28, 2000 which addressed the manner in which the Agency

calculated dislodgeable foliar residue and turf transferable residue levels for use in the risk assessment. The Agency's response can be found in the June 27, 2000 memo from Jeff Dawson, Health Effects Division. Note that the analyses completed by both the Agency and BASF indicate that current label requirements for a 12 hour Restricted Entry Interval should be significantly lengthened. BASF has proposed REIs that range from 5 to 22 days in agriculture and from 4 to 14 days on ornamentals while the Agency calculated risks would likely result in still longer REIs. EPA will accept the REI values proposed by BASF based on the curve-fitting approach if data are collected on the remaining crops to confirm the analysis. Jeff Dawson writes, "If confirmatory data are not collected, risk managers should carefully consider the use of the psuedo-first order analysis completed by the Agency in light of the unique attributes of the data currently available for vinclozolin". The Agency does not concur with the BASF use of turf transferable residue (TTR) data for the toddler turf risk assessment and will continue using the risk values calculated in the February 8, 2000 Agency risk assessment.

BASF Comment 5. BASF objected to the use of the 25.2% dermal penetration factor for dermal risk assessment. In addition, they object to summing the percentage dermal penetration from the 10 hour exposure (13.3%) with percentage of vinclozlin remaining in the skin (11.9%) and that the vinclozolin remaining in the skin would not likely be completely absorbed within 24 hours.

BASF submitted in vitro dermal studies on rat skin, in vivo studies in rat skin, and in vitro studies with human skin showing that the human skin absorbed about 4x less than rat skin.

Response to Comment 5. OPP has data demonstrating that pesticides remaining on or in the skin continue to be absorbed. A worker exposed to vinclozolin would absorb a percentage of vinclozolin and vinclozolin remaining in the skin would continue to be absorbed. Vinclozolin remaining in the skin would continue to contribute to exposure analogous to human exposure.

OPP reviewed these *in vitro* studies and found that they were conducted in an acceptable manner. However, OPP will accept *in vitro* studies as a suitable alternative to *in vivo* studies only on a case by case basis, and only when the registrant adequately demonstrates that the dermal penetration from *in vitro* studies gives comparable values to *in vivo* dermal penetration. It is noted that the *in vitro* dermal studies in the rat did not give comparable values to the *in vivo* dermal studies in the rat, and that use of the ratio in the rat skin to human skin needs validation for vinclozolin.